REMARKS

This amendment is in response to the Non-Office Action mailed March 21, 2007.

Claims 1-9, 11-14, and 24-25 are under current examination. Claims 15-17 and 19-23 have been withdrawn by the Examiner. Claim 10 has been withdrawn by the Applicant. Claim 18 has been cancelled without prejudice. Claim 1 has been amended. No new matter has been added by the amendments.

A Petition for a Two (2) Month Extension of Time under 37 C.F.R. §1.136(a) is enclosed herewith along with a check for $450.00 to cover the large entity fee as per 37 C.F.R. §1.17(a)(2).

Applicant acknowledges with appreciation the Examiner's withdrawal of the previous objection to the specification as well as the withdrawal of the rejection of claim 25 under 35 U.S.C. §112, second paragraph.

§112 REJECTIONS

The Examiner has maintained the rejection of claims 5-6 and 8 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully disagrees with the rejection.

With regards to claims 5-6 and 8, it appears the Examiner is of the opinion that the differences in apoptosis are caused by the absence of E1A function in the AdΔ24-p53 virus as used in Figure 7. Applicant has carefully considered the Examiner's remarks but respectfully disagrees. To clarify, the AdΔ24-p53 virus comprises a 24 bp deletion in the pRb-binding CR2 domain of the E1A gene. This deletion affects binding of E1A to Rb but does *not* render the resulting virus an E1A-negative virus. Said deletion does not

comprise the amino terminus of E1A. Rather, as is presented in Figure 1 of Fueyo et al. (Oncogene 19: 2-12 (2000); hereinafter referred to as Fueyo), said deletion is located in a second Rb-binding region in the carboxy-terminal half of the E1A protein. Thus, the amino terminus of the resultant E1A protein, which is required for the induction of cellular DNA synthesis, is ***intact*** in the AdΔ24 virus.

Furthermore, as clearly evidenced by Fueyo, AdΔ24 mutant viruses are able to replicate in and lyse cancer cells (*see*, for example, the Abstract of Fueyo).

Therefore, AdΔ24 virus encodes a functional E1A protein and is *not* an E1A-negative virus.

Moreover, lysis of cancer cells infected by AdE1 encoding wildtype E1A protein is equally enhanced by p53 expression as is the lysis of cells infected with AdΔ24 viruses. Example 4 (pages 47-49 of the application as filed) clearly shows that co-infection of p53-encoding viruses with AdE1 encoding wildtype E1A protein and with AdΔ24 viruses results in a 10-100-fold enhancement of oncolysis in SaOs-2 cells, A549 cells and U373MG cancer cells. This clearly shows that the enhancement of apoptosis in cancer cells by p53 is observed both with wildtype E1A and with E1A-Δ24.

Significantly, the observed apoptosis was **less** upon co-infection of p53-transducing virus with the AdΔ55K virus, comprising a deletion in the gene encoding E1B-55K protein. Thus, the enhancing effect of E1B-55kDa protein is clearly demonstrated and the subject matter of claims 5-6 and 8 is thus enabling. Withdrawal of the §112 rejection is therefore kindly requested.

§102 REJECTIONS

Applicant infers the Examiner's apparent withdrawal of the §102 rejections of claims 1-7, 14 and 24 as being anticipated by Chang et al.

The §102 rejection against claims 1-2, 9 and 24-25 as being anticipated by Fueyo was maintained.

In an effort to advance prosecution and further distinguish from Fueyo, Applicant has amended claim 1 to recite, *inter alia*:

"...a conditionally replicating adenovirus and provided in the genome thereof with the coding sequence of at least one restoring factor functional in restoring the p53 apoptosis pathway in said target cells ... wherein said restoring factor induces at least one of accelerated cell lysis and a faster release of virus progeny, compared to a recombinant adenovirus lacking said coding sequence."

The amendment is supported by the specification, e.g., on page 16, lines 29-35 of the application as filed.

Fueyo provides cells with an adenovirus having an E1A Δ24 protein that is no longer capable of binding Rb. However, Applicant respectfully asserts that Fueyo fails to disclose, suggest or make any mention of at least an adenovirus provided with a coding sequence for at least one restoring factor whereby said restoring factor induces at least one of accelerated cell lysis and a faster release of virus progeny, compared to a recombinant adenovirus lacking said coding sequence, essentially as claimed in claim 1. Applicant believes that the rejection of claim 1 as being anticipated by Fueyo is overcome in view of the amended claim 1. Claims 2, 9 and 24-25 depend from and include all the limitations of claim 1. Therefore, withdrawal of the §102 rejections of claims 1-2, 9 and 24-25 is kindly requested.

§103 REJECTIONS

The examiner rejected claims 1 and 11-13 in view of Lin et al. and Chang et al. alleging that the combination of Lin and Chang would also teach adenoviral-mediated induction of apoptosis in cells that are hampered in the p53-dependent pathway (*see* also below). Applicant respectfully asserts that this rejection has become moot in view of amended claim 1, which now recites, *inter alia*, that the adenovirus encodes a restoring factor that induces at least one of accelerated cell lysis and a faster release of virus progeny, compared to a recombinant adenovirus lacking said restoring factor.

Therefore, applicant kindly requests withdrawal of this rejection.

Claims 1-8, 11-14 and 24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Lin et al. (Cancer Research. Oct. 15, 2000.60.p.5895-5901), hereinafter Lin, in view of Chang et al. Applicant respectfully disagrees.

The Examiner concedes that Chang does not explicitly teach that target cells are hampered in the p53 dependent apoptosis pathway but alleges that Lin teaches restoration of p53 dependent apoptosis. Specifically, the examiner refers to the results section on page 5896 of Lin et al. where the results of transcriptional activation assays are discussed. In the first set of experiments, p53 and p53 14/19 are transfected into cells that lack p53, and the activity of reporter constructs comprising luciferase under the control of a P21WAF-1 (Figure 1A) or BAX promoter (Figure 1B) is determined. It is concluded that p53 14/19 induces transcriptional activation of P21WAF-1 and BAX-promoters to similar levels in H1299 and p53-/- MEF cells, which both lack endogenous p53 protein.

In a second set of experiments in Lin, p53 and p53 14/19 are tranduced by adenoviral infection into cells that lack p53 or that lack both p53 and *mdm2,* followed by

monitoring of the protein levels of P21WAF-1 and BAX. The conclusion is that p53 14/19 induces protein levels of P21WAF-1 and BAX to a similar extent as wildtype p53 in H1299 (Figure 1C) and in p53-/-, mdm2-/- (Figure 1D).

However, Lin fails to disclose or suggest at least one restoring factor functional in restoring a p53 apoptosis pathway in target cells hampered in a p53 dependent apoptosis pathway, essentially as claimed in claim 1. None of the above-mentioned experiments in Lin show that p53 and/or p53 14/19 induces apoptosis in cells lacking endogenous p53 protein. Rather, the entire article of Lin is concerned with inhibiting oncogenic transformation of cells (*see* abstract of Lin), **not** with apoptosis. Moreover, neither Lin nor Chang disclose or suggest whereby said restoring factor induces at least one of accelerated cell lysis and faster release of virus progeny, essentially as claimed in claim 1. In particular, Lin's experiments do not teach or show cell lysis and/or release of virus in cells transduced with adenovirus with and without said p53 or p53 14/19 protein, nor do they in any way suggest that such an effect would be provided by incorporating the p53 14/19 into a replication in competent adenovirus.

Accordingly, claim 1 is believed to be patentable and nonobvious over Lin in view of Chang. Claims 2-8, 11-14 and 24 depend from and include all the limitations of claim 1 and are thus believed to be patentable and nonobvious for at least the reasons given above for claim 1. Applicant therefore kindly requests withdrawal of all the §103 rejections.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that claims 1-9, 11-14, and 24-25 are patentable and nonobvious over the cited references. Consequently, the Applicants respectfully request reconsideration and withdrawal of the objections and rejections and allowance of the application. Such early and favorable action is earnestly solicited.

A Petition for a Two (2) Month Extension of time and corresponding large entity fee for same is enclosed herewith. It is believed that no additional fees or charges are currently due. However, in the event that any additional fees or charges are required at this time in connection with the application, they may be charged to applicant's representatives Deposit Account No. 50-1433.

Respectfully submitted,
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Dated: 8/21/07